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EXAMINER	
GOLDBERG, JEANINE ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/976,423	HOGAN, KIRK	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed July 13, 2010. Currently, claims 72-112 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action is FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 72-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) and Pharmacogenetics (Chapter 4, pages 309-326) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) further in view Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) and Anderson et al (US Pat. 6,267,722, July 31, 2001) and further in view of Miller (Anesthesia, Vol. 2, pages 1323-

1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994).

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Further, with regard to the limitation that the kits contain instructions for using said kit for generating said perioperative genomic profile for said subject, the inclusion of instructions is not considered to provide a patentable limitation on the claims. See In re Ngai, 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004) (holding that an inventor could not patent known kits by simply attaching new set of instructions to that product).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with **BchE** deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). La Du teaches specific variants in the Butyrylcholinesterase gene.

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of **CYP2D** gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches that the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactivation of drug substrates (page 487, col. 2). Evans also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-

metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1). Evans specifically suggests making a DNA array for automated, high-throughput detection of functionally important mutation in genes that are important determinants of drug effects such as drug-metabolizing enzymes. The suggested genes on the array include **TNF, MTHFR and CYP2D6**, for example (see figure 3).

Thus, the prior art clearly illustrates that the claimed genes are known to be related to resistance to anesthesia.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a

particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia illustrates the design of probes and oligonucleotides for detection of single nucleotide substitutions and variations. As seen in Figure 3, for example, 25 overlapping 25-base probes are affected by changes in a single target nucleotide. Moreover, Hacia teaches that the analysis is completed by scanning for variation and evaluation using an algorithm (page 44)(i.e. a computer program directing the processor to analyze the data). As seen in Figure 5, the data is outputted from a computer program to illustrate the detection of polymorphisms.

With respect to kits, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared. Ahern teaches kits may comprise instructions that provide researcher detailed instructions to follow.

Anderson et al. (US Pat 6,267,722, July 31, 2001) teaches point of care diagnostic systems. Anderson teaches the systems are designed to accept input in the form of patient data, including, but not limited to biochemical test data, physical test data, historical data and other such data, and to process and output information, preferably data relating to a medical diagnosis or a disease risk indicator. The patient data may be contained within the system, such as medical records or history, or may be input as a signal or image from a medical test or procedure, for example, immunoassay test data, blood pressure reading, ultrasound, X-ray or MRI, or introduced in any other form. Specific test data can be digitized, processed and input into the medical diagnosis expert system, where it may be integrated with other patient information. The output from the system is a disease risk index or medical diagnosis.

Finally, the art teaches a rationale for combining reagents for these genes associated with these conditions into a kit. Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that “it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery”. Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the necessary reagents for

sampling patients prior to subjecting the patient to anesthetics for the presence of alleles within the CYP2D6, or BCHE genes which cause resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, or Evans and thus avoiding any fatal reaction to the anesthesia, for example.

As discussed above, AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evans also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3).

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, or

desbrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have packaged reagents needed to screen individuals to determine the genetic composition of the individuals to provide individualized diagnosis and to avoid any fatal reaction to the anesthesia in a quick and efficient cost effective kit.

Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Quane especially teaches a mutation associated with surgical conditions and states once the mutation is detected, administering anesthesia to patients susceptible to conditions can be avoided. The skilled artisan would similarly apply this rationale to other mutations associated with surgical conditions. Specifically, codeine should be administered with care to individuals having certain CYP2D6 mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete

picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

In summary, the prior art teaches

- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (De Lu, AAS, Poort, Evans, for example)
- Once a mutation is known to be associated with negative response to anesthesia or drugs, patients with the mutation can avoid the negative response (Quane)
- Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia)
- Packaging reagents into a kit saves time and money (Ahern)
- The prior art teaches the use of computer programs for systems of diagnostic care for outputting patient information and risk index (Anderson)

Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money and included a computer program taught by Anderson for the digitization, integration and convenience of patient information, and risk index.

Response to Arguments

The response traverses the rejection.

The response cites numerous passages from the prior Decision on Appeal mailed July 31, 2006 to support the limitation of kits containing instructions is supported by the disclosure (pages 20-21 of response filed September 24, 2009). It is noted that the instant rejection is an obvious type rejection and not a new matter rejection, as was addressed by the Board. The Board made no comment on the propriety of In re Nagai. In fact the Board specifically suggested to the Examiner to consider the prior art of record for 09/613,887.

The response suggests that the references did not teach or suggest a computer program comprising instructions which direct a processor to analyze data derived from said reagents. While the response asserts that silence in the Board's decision is acquiescing to applicant's position, this argument has been reviewed but is not persuasive, as there is no indication of the Board's position on this matter or record.

The response filed December 18, 2007, September 24, 2009 and July 13, 2010 reiterates many of the previously addressed arguments. The first two points, appear to address In re Ngai and the Board's apparent position. The Board does not provide any statements on In re Ngai that would be appropriate in considering the newly presented rejection, as above. The response asserts that the kits are not "known kits" (see page 14 of the response filed July 13, 2010). This argument has been reviewed but not convincing, because in light of the teachings in the art, the kits would have been obvious. Fourth, the response asserts the Examiner has not indicated where kits are to be found. This argument has been reviewed but is not convincing. Kits are routine in the art for simplicity. The examiner specifically included the Ahern reference to address

applicants concerns that kits were not known at the time the invention was made. The response argues that Ahern discourages use of kits (see page 23 of response filed September 24, 2009; page 15 of the response filed July 13, 2010). This argument has been reviewed but is not persuasive. Reviewing the complete disclosure of Ahern specifically encourages commercialization of kits so scientists can quickly, cheaply order the necessary reagents for a particular method.

Applicant's fifth argument is directed to the printed matter of In re Ngai vs the computer program comprising instructions directing a processor to analyze data derived from such reagents (see page 16 of the response filed July 13, 2010). This argument has been reviewed but is not persuasive. The instructions as intended use in the kit of Ngai and the instructions on a computer program as indented use in the instant application are analogous. Applicant appears to be attempting to place instructions in a different format, i.e. a computer to frustrate the intent of Ngai. The response further asserts that Anderson does not remedy the defects. The response asserts that Anderson does not teach a computer program comprising instruction which direct a processor to analyze data derived from use of "said reagents." (see page 17 of the response filed July 13, 2010) This argument has been reviewed but is not convincing. Anderson specifically takes results from various tests including biochemical tests, like the instant test/reagents, and outputs data. Thus in view of the teachings in the art, it would have been obvious to take test results from the combined methods of Acta Anaesthesiologica Scandinavica and La Du and Pharmacogenetics and Evans et al in

view of Hoon et al. and Hacia and place the reagents in a kit and design a computer program, as in Anderson, to analyze the output.

The response further asserts that the rejection fails to address the content of the kits' instructions as provided in Claims 82-84, 101, 106, 107, for example (see page 19 of the response filed July 13, 2010). As noted above, the information provided in the form of instructions in a kit does not carry patentable weight, as held in Ngai.

The response asserts that the references do not suggest kits to detect the presence of variant alleles in two or more genes (see page 19 of the response filed July 13, 2010). This argument has been reviewed but is not persuasive. The rejection clearly considers analyzing two or more variant alleles, see Hacia and Hoon. Further, the rejection clearly considers placing reagents from a method into a kit for ease and cost-effectiveness.

The response asserts Ahren teaches away from kits for characterization of DNA. This argument has been thoroughly reviewed and is not convincing. Kits for DNA characterization are overwhelmingly prevalent in the art. Nearly every patent application directed to DNA characterization includes discussion of kits for reagent. The response cites a sentence in Ahern that suggests that designing primer sets for sequencing is daunting and it makes more sense to hire out. This specifically illustrates that companies that can make kits with reagents are desirable to those scientists seeking to characterize DNA, for example. This demonstrates the need for kits because it is "daunting for many scientists and it makes more sense to hire out." Thus

companies would be motivated to package reagents in a kit to sell to scientists who find it daunting to make the reagents for the method themselves.

The response asserts that none of the references teach components sufficient to detect variant alleles. The response asserts that what is missing from the references is a disclosure of primers and probes specific to the genes. It is noted that the claims are not drawn to primers or probes to the genes. The claims are drawn to reagents. Each of the references of Acta Anaesthesiologica Scandinavica and La Du and Pharmacogenetics and Evans et al discuss methods for genotyping of the mutant alleles. Evans specifically teaches an array for detecting the variants; AAS teaches genotyping using sequencing and enzymes.

The response asserts there is no motivation to combine the references (see page 20 of the response filed July 13, 2010). The response further states that there is no explicit or implicit teaching or suggestion or motivation to combine element present in the art to generate the presently claimed invention (see page 21 of the response filed July 13, 2010). *KSR v. Teleflex*, 550 U. S. 398 (2007): In a unanimous opinion authored by Justice Kennedy, the Supreme Court held that the Federal Circuit's "narrow" & "rigid" TSM test is not the proper application of the nonobviousness doctrine of Section 103(a) of the Patent Act. "To facilitate review, [the obviousness] analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ." An obviousness determination is not

the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Thus, given KSR, the references are not specifically required to provide the motivation. The teaching suggestion and motivation may be the common sense of those skilled in the art would employ. Thus, as is here, the ordinary artisan would be motivated to have gathered the reagents necessary for determining alleles associated with poor outcomes to surgery into a kit for the benefits of a kit. In particular Quane teaches specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be ***avoided*** (page 471, col. 2)(emphasis added). The ordinary artisan would have been motivated to have determined alleles in genes that are known to trigger symptoms caused by anesthesia that should be avoided. Moreover, including a computer program for the expected benefits of digitizing, processing and inputting the information into the medical diagnosis expert system, where it may be integrated with other patient information. The output from the system is a disease risk index or medical diagnosis. The response asserts there is no teaching regarding the kits and computer programs of the present invention. This argument has been reviewed but is not deemed persuasive. As outlined above in detail:

- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative/anesthesia drugs (De Lu, AAS, Poort, Evans, for example)
- Once a mutation is known to be associated with negative response to anesthesia or drugs, patients with the mutation can avoid the negative response (Quane)
- Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia)
- Packaging reagents into a kit saves time and money (Ahern)
- The prior art teaches the use of computer programs for systems of diagnostic care for outputting patient information and risk index (Anderson)

Thus, the combination of references taught in the art would have rendered obvious the ordinary artisan the claimed invention. The response asserts the Quane reference is irrelevant because none of the claims require RYR1 gene. This argument has been reviewed but is not deemed persuasive. Although RYR1 is not included within the large list of genes within the scope of the claims, RYR1 is within the same genus of genes that are associated with poor response to anesthetics as the claimed genes. Thus, the ordinary artisan would have appreciated that avoiding any negative responses to anesthetics would have been optimal and would have been motivated to have extended the concept of avoiding drugs known to be associated with death or poor responses to other genes associated with anesthesia response and death. The response asserts that Quane does not refer to DNA testing for avoiding MH susceptibility. This argument has been reviewed but is not deemed persuasive. Reading Quane as a whole, the ordinary artisan would have appreciated that Quane teaches that Quane is seeking other genetic factors influencing triggering of MH in susceptible individuals. Quane

immediately transitions into the biochemical studies of RYR1 gene and the mutations found in the gene. Quane finds that the majority of patients “diagnosed as MHE by the IVCT may not be susceptible to MH from a genetic viewpoint." Quane continues that "such a patient should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia.” (page 473, col. 2). Thus, contrary to the response’s assertions, Quane explicitly does refer to DNA testing for avoiding MH susceptibility.

The declaration and response appear to state that the skilled artisan in this case was a clinical anesthesiologist. The response states the Office recognizes an anesthesiologist as one of ordinary skill in the art (pages 29-31 of the response filed September 24, 2009). This argument is reviewed. While the Examiner agrees that an anesthesiologist may be one of ordinary skill in the art, the Examiner also recognizes the biochemical authors of Quane, AAS, LaDu, Evans and Pharmacogenetics as ones of skill in the art. Quane clearly recognized the benefit of testing an individual prior to surgery to avoid triggering MH. The skilled artisan would encompass molecular biologists studying the relevant relationships. Thus, the skilled artisan would have been aware of the solution, as evidenced by the articles by molecular biologists. The response asserts that the rejection fails to place the prior art of record in the hands of the skilled artisan and that they would then have arrived at the invention. The MPEP clearly states that the requirement is that " if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited

references, they would still be unable to solve the problem." Here, the declaration and arguments appear to suggest that the anesthesiologists were not placed in the situation. However, the question relies upon 'if' the references were known by the anesthesiologists, would they be unable to solve the problem. The response filed July 13, 2010 cites to Dr. Hogan's declaration and states that "anesthesiologist of ordinary skill were not aware of, and did not use, kits for genomic analysis of single or multiple polymorphisms or diseases." (pages 27-28 of the response filed July 13, 2010). Skill in the art not limited to anesthesiologist but also encompasses molecular biologists. Thus, it would have been obvious to molecular biologists who were working on association studies that demonstrated poor response to anesthesia to analyze patients for the polymorphisms that affect poor response. Identifying patients that may have poor response appears to be their purpose for analysis.

The response has submitted a newsletter article "Perioperative Genomics: Anesthesiology Goes Molecular", GenomeLife Magazine, Issue 3, November 2003, page 7. The response asserts that there is a wide separation between anesthesiology and genome based medicine. It is noted that the article is from 2003. The article further acknowledges that the idea of perioperative genomics is "simple: since millions of common variants (polymorphisms) in our DNA have been catalogued, it should now be possible to examine specific DNA changes in order to predict negative surgical outcomes such as intraoperative bleeding." This appears to support the position that if references describing variants associated with negative surgical outcomes were placed

in the hands of the skilled artisan, the claims would have been obvious. The GenomeLife Magazine article acknowledges the simplicity of the idea given the variants known to be predictive of negative surgical outcomes. This is precisely the type of references cited in the above rejection and thus, it would have been "simple" to the skilled artisan given the cited references.

Although the reference notes a "separation of the practice of anesthesiology from clinical genetics and genome-based medicine" this does not negate the obviousness to one of ordinary skill in the either the biochemical fields or the anesthesiology fields. The GenomeLife reference even notes that the use of biochemical studies could predict perioperative outcomes based on preoperative genomic information, something that Quane noted years earlier.

The response submits a declaration by Dr. Hogan to discuss the non-obviousness of the claimed kits. It is noted that "the weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); cf. In re Alton, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered)." Here the declaration does not appear to provide any evidence.

The declaration by Dr. Hogan appears to assert the claimed invention meets a long felt need. The response filed July 13, 2010 states that Dr. Hogan's Declaration provides "clear-cut, expert, and uncontested evidence that artisans of ordinary skill have been highly motivated to detect multiple risks….for many decades… (see page 30 of the response filed July 13, 2010). The declaration under 37 CFR 1.132 filed December 18, 2007 is insufficient to overcome the rejection of claims as set forth in the last Office action because: It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references; they would still be unable to solve the problem. See MPEP § 716.04. The declaration appears to be focusing on the fact that anesthesiologists did not arrive at the kits. However, the standard required is that one of skill in the art. One skilled in the art would encompass molecular biologists who were performing association studies between the polymorphisms and poor reactions to anesthesiology. The declaration provides that anesthesiologists were not aware of the kits, however the standard to meet non-obviousness under long-felt need requires that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. Thus, applicant's declaration to provide that the invention meets a long felt need does not address all of the elements for a showing of non-obviousness under long-felt need.

Appellant then turns to Dr. Coursin's declaration to explain there was no suggestion or teaching in the prior art or elsewhere for the perioperative genomic profiles of the presently claimed invention. It is noted that Dr. Coursin uses the word "novel" which is associated with novelty and not obviousness. Dr. Coursin states he is unaware of any one previously proposing or disclosing perioperative genomic profiles. This passage was thoroughly considered but not found sufficient to overcome the prima facie case of obviousness. Extensive motivation to combine the cited references is given in the rejection.

The response further provides a declaration by Dr. Coursin directed to long-felt need. Similar to the declaration provided by Dr. Hogan, the declaration under 37 CFR 1.132 filed December 18, 2007 is insufficient to overcome the rejection of claims as set forth in the last Office action because: It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by

another before the invention by applicant. Third, the invention must in fact satisfy the long-felt need.

The declaration states in paragraph 3, that none one taught or suggested perioperative genomic profiles before the present patent application. It is noted that the claims are drawn to kits. The kits have intended use for perioperative genomic screening, however the intended use does not carry patentable weight. Further, it is noted that at the time the invention was made, genomic profiles were generically known. In fact, Evans teaches molecular diagnostic arrays for analyzing functionally important mutations including MTHFR, CYP2D6. Therefore, profiling using arrays was known before the present application.

The declaration appears to suggest that that the long felt need was recognized prior and was persistent. The response argues that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before." A close reading of the passage in Dr. Coursin's declaration appears to state something different. The declaration appears to state that Dr. Coursin has been practicing Anesthesiology for 26 years. This is much different than he has been trying to solve the problem of detecting multiple risks for complications with genetic variations, as characterized by the brief (page 27 of the brief filed September 24, 2009). The passage cited by the brief does not even use the words genetic variations.

In the event that a narrow reading of the problem is taken, i.e. a need for nucleic acid based perioperative screening, the response, prosecution history and declarations

appear to state that the anesthesiologists and skilled artisans, as defined by the application, did not recognize the need prior to the invention. The declaration by Dr. Hogan states that anesthesiologist of ordinary skill were not aware of kits or genomic analysis of polymorphisms and diseases. This situation appears analogous to the situation presented in the MPEP. The need must have been a persistent one that was recognized by those of ordinary skill in the art. In re Gershon, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware.") Thus, since the art did not apparently recognize or was aware of this problem for a nucleic acid based perioperative screening method, it could not be a long-felt problem.

In the event that a broader reading for the problem is presumed, i.e. the problem of perioperative screening, the declaration appears to support a solution for this problem. The declaration filed by Dr. Coursin states in paragraph 4, that surgeons and anesthesiologist were highly motivated to detect multiple risks for complications during a surgical procedure associated with genetic variations and ask patients whether any family members had complications during surgery or anesthesiology. This appears to suggest that the long felt need had been satisfied using a survey prior to the instant

application. Thus, the problem had been satisfied by another means before the invention.

Here, the declaration of Dr. Coursin fails to provide any evidence in the opinion declaration that the ordinary skilled artisans were working on the problem and for how long. The declaration fails to provide any evidence that those working in the art on the problem knew of the Quane, Miller, Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans et al, Poort et al , Hoon et al. or Hacia references and were still unable to solve the problem.

The response argues that the rejection fails to place in the hands and minds of the appropriate skilled artisan the prior art of record and the mental and experimental process for modifying the art to arrive at the inventions (page 35 of response filed September 24, 2009). *In re Winslow* discuses that we should "first picture the inventor as working in his shop with the prior art references- which he is presumed to know- hanging on the walls around him." *In re Winslow*, 365 F.2d 1017 (CCPA 1966). The court in *Winslow* continues "[s]ection 103 requires us to presume full knowledge by the inventor of the prior art in the field of his endeavor." Here, the ordinary artisan working in "his shop" would be apprised of each of the references. Moreover, extensive guidance is given in the rejection as to how the references would be combined to arrive at the claimed invention.

In paragraph 6 of Dr. Coursin's declaration, Dr. Coursin states that there are unexpected results. This argument has been reviewed but is not persuasive. The declaration states that there was significant genetic heterogeneity present in most patients. This is not unexpected. In fact it is completely expected. The art of record teaches various frequencies of polymorphisms and also discusses personalized medicine. At the time the invention was made, the state of the art recognized the variation between individuals in populations. Further, the declaration states that the perioperative genomic profiles identified many patients that were not accounted for using contemporary tools for detection. Again, this is not unexpected, it is completely expected that patients with no family history have polymorphisms that result in poor outcome. There are many patients who have no known family history, but yet have problems with surgery or anesthesia. Thus, it is not unexpected that there is a genetic basis for these cases. Furthermore, it is noted that the claims are not commensurate in scope with any "unexpected results".

The declaration in paragraph 7 asserts that if the perioperative genomic profiles were obvious, the practitioners would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. This argument has been reviewed but is not persuasive. The rejection is made under 103 and not 102. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This illustrates that the art does not have to arrive at the claims but merely render the claims obvious.

It is noted again, the claims are drawn to products with intended use. The claims are not drawn to methods for perioperative genomic profiling.

5. Claims 108-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) and Pharmacogenetics (Chapter 4, pages 309-326) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) further in view Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) and Anderson et al (US Pat. 6,267,722, July 31, 2001) and further in view of Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994) as applied to claims 72-107 above and further in view of the specification (Tables 1-4).

AAS, LaDu, Pharmoacogenetics, Evans, Hoon, Hacia, Ahern, Anderson, Miller and Quane do not specifically teach profiling for each of BchE, CYP2D6, MTHFR, MTR, CBS, F2 (also known as Prothrombin), F5, CACNA1S, CYTP2, TNFA and TNFB.

However, the instant specification teaches markers in each of these genes which are associated with various operative related disorders (see pages 55-57 of the specification reproduced below, Tables 1-5). The specification clearly illustrates genes and mutations which are associated with the particular mutations in the prior art. The specification thus provides references for BChE, CYP2D6, MTHFR, MTR, CBS, MTRR, F5, F2 (prothrombin), CACNAIS, TNFa and TNFb.

Table 1
Butyrylcholinesterase Deficiency Markers

Gene	Mutation	% Incidence (homozygote/heterozygote)	Reference
BChE	A209G	.05/4 "atypical"	Cell. Mol. Neurobiol., 11:79 [1991]
BChE	G1615A	1.3/22 "K-Variant"	Cell. Mol. Neurobiol., 11:79 [1991]

Table 2
Poor Debrisioquine Metabolism Markers

Gene	Mutation	% Incidence (homozygote/heterozygote)	Reference
CYP2D6	G1934A	66% of poor metabolizers	Am. J. Hum. Genet., 60:284 [1997]
CYP2D6	deletion	17% of poor metabolizers	Am. J. Hum. Genet., 60:284 [1997]
CYP26D	A2637del	4% of poor metabolizers	Am. J. Hum. Genet., 60:284 [1997]
CYP2D6	T1975del	% of poor metabolizers	Am. J. Hum. Genet., 60:284 [1997]

Table 3
Markers for Thrombus Formation

Gene	Mutation	% Incidence (homozygote/heterozygote)	Reference
MTHFR	C677T	12%/>30%	Nature Genet., 10:111 [1995]
MTHFR	A1298C		Nature Genet., 10:111 [1995]
MS (MTR)	A2756	2%/35%	Genet. Epidemiol., 17:298 [1999]
CBS	Intron 7 68 bp insertion	1%/12%	Am. J. Hum. Genet., 59:1262 [1996]
MTRR	A66G	29% (allele frequency)	Atherosclerosis 157:451 [2001]
F 5 Leiden	G1691A	6% of population	New Eng. J. Med., 336:399 [1997]
Prothrombin	G20210A	2% of population	New Eng. J. Med., 341:801 [1999]

Table 4
Markers for Malignant Hyperthermia

Gene	Mutation	% Incidence (homozygote/heterozygote)	Reference
RYR1	G6502A	7% of MH cases	Hum. Mol. Genet., 8:2055 [1999]
RYR1	G1021A	6-10% of MH cases	Hum. Mol. Genet., 8:2055 [1999]
RYR1	C1840T	4% of MH cases	Hum. Mol. Genet., 8:2055 [1999]
RYR1	C6487T	4% of MH cases	Hum. Mol. Genet., 8:2055 [1999]
RYR1	G7303A	4% of MH cases	Hum. Mol. Genet., 8:2055 [1999]
RYR1	C7373A	4% of MH cases	Hum. Mol. Genet., 8:2055 [1999]

CACNA1S	G3257A	4 families	Am. J. Hum. Genet., 60:1316 [1997]
CPT2	C2023T	3 families	Am. J. Hum. Genet., 20 A5 [1998]

Table 5
Markers for Inflammatory Response

Gene	Mutation	% Incidence (homozygote/heterozygote)	Reference
TNFα	G-308A	16% allele frequency	Neurology 54:2077 [2000]; JAMA 282:561 [1999]
TNFβ	G+252A	65% allele frequency	Neurology 54:2077 [2000]; JAMA 282:561 [1999]

The response filed March 26, 2001 in the parent application specifically illustrates that the invention does not claim discovery of newly identified DNA sequences (page 7). The response in response to a Written Description rejection stated "[t]he invention does not claim discovery of newly identified DNA sequences..." As such, it is clear from the prosecution history and the specification none of the genes required for Claims 108-112 are newly associated with operative mutations.

Therefore, it would have been obvious in view of the teachings of the references from the specification, AAS, LaDu, Pharmoacogenetics, Poort, Hoon, Hacia, Ahern, Anderson, Miller and Quane to include the recited genes along with additional genes on the array of Hacia for the highthroughput analysis of operative complications. The ordinary artisan would have desired to compile all known genes that are associated with

operative complications on a high throughput array to detect mutations known to affect decisions.

Response to Arguments

The response traverses the rejection. The response asserts the rejection fails to teach all the limitations for the reasons discussed above and there is no motivation to combine the references. This argument has been considered but is not convincing for the reasons provided above.

The response further argues that the claimed set of markers would not have been obvious opposed to the innumerable number of other possible combinations of markers in the literature. The instant claims are directed to open claim language that permits the inclusion of each of the claimed markers in addition to other markers. The recited mutations may be only a few of many markers included on the array of Hacia. The ordinary artisan would have been motivated to have included all genes or markers relevant to anesthesia to generate a high throughput analysis of all operative complications.

Thus for the reasons above and those already of record, the rejection is maintained.

6. Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) and Pharmacogenetics (Chapter 4, pages 309-326) and Evans et al (Science, Vol. 286, pages 487-491,

October 1999) in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) further in view Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) and further in view of Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with **BchE** deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle

relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). La Du teaches specific variants in the Butyrylcholinesterase gene.

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of **CYP2D** gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches that the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactivation of drug substrates (page 487, col. 2). Evans also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity

occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1). Evans specifically suggests making a DNA array for automated, high-throughput detection of functionally important mutation in genes that are important determinants of drug effects such as drug-metabolizing enzymes. The suggested genes on the array include **TNF, MTHFR and CYP2D6**, for example (see figure 3).

Thus, the prior art clearly illustrates that the claimed genes are known to be related to resistance to anesthesia.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia illustrates the design of probes and oligonucleotides for detection of single nucleotide substitutions and variations. As seen in Figure 3, for example, 25 overlapping 25-base probes are affected by changes in a single target nucleotide. Moreover, Hacia teaches that the analysis is completed by scanning for variation and evaluation using an algorithm (page 44)(i.e. a computer program directing the processor to analyze the data). As seen in Figure 5, the data is outputted from a computer program to illustrate the detection of polymorphisms.

With respect to kits, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared. Ahern teaches kits may comprise instructions that provide researcher detailed instructions to follow.

Finally, the art teaches a rationale for combining reagents for these genes associated with these conditions into a kit. Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller

teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to

triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the necessary reagents for sampling patients prior to subjecting the patient to anesthetics for the presence of alleles within the CYP2D6, or BCHE genes which cause resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, or Evans and thus avoiding any fatal reaction to the anesthesia, for example.

As discussed above, AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evans also teaches “the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that

require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3).

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, or desbrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have packaged reagents needed to screen individuals to determine the genetic composition of the individuals to provide individualized diagnosis and to avoid any fatal reaction to the anesthesia in a quick and efficient cost effective kit.

Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these

conditions to arise. Quane especially teaches a mutation associated with surgical conditions and states once the mutation is detected, administering anesthesia to patients susceptible to conditions can be avoided. The skilled artisan would similarly apply this rationale to other mutations associated with surgical conditions. Specifically, codeine should be administered with care to individuals having certain CYP2D6 mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

In summary, the prior art teaches

- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (De Lu, AAS, Poort, Evans, for example)
- Once a mutation is known to be associated with negative response to anesthesia or drugs, patients with the mutation can avoid the negative response (Quane)
- Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia)
- Packaging reagents into a kit saves time and money (Ahern)

Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts the rejection fails to teach all the limitations for the reasons discussed above and there is no motivation to combine the references. This argument has been considered but is not convincing for the reasons provided above.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable over the art.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is

(571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
September 29, 2010